REMARKS

Claims 2-19, 35, and 37 have been cancelled. Claim 1 has been amended. Claims 1, 20-34 and 36 are now pending in this application. Support for the amendments is found in the existing claims and the specification as discussed below. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Interview

Applicant thank Examiner Li and her Supervisor Examiner Campell for the courtesy of a personal interview on October 13, 2006 with Dan Altman and the undersigned. The interview is summarized on pages 5-6 herein.

Inventorship

As mentioned during the interview, a request to correct inventorship under 37 C.F.R. § 1.48(b) was submitted on August 23, 2005. Accordingly the invention should now be in the name of Thomas Stegmann as sole inventor.

Priority

The Office Action states in item 4 that claims 12, 17, and 37 are considered to have an effective filing date of August 27, 2003. The effective filing date of claims 1, 20-34 and 36 was determined as July 24, 1998. Claims 12, 17, and 37 are cancelled with this amendment. Accordingly, the remaining claims (claims 1, 20-34, and 36) all have an effective filing date of July 24, 1998.

Rejection under 35 U.S.C. § 103(a) (Htun, Linemeyer, and Kordyum)

Claims 12, 17, and 37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Htun, et al. (J. Mol. Cell. Cardiol. April 1998, Vol. 30: 867-877), Linemeyer, et al (US Patent No. 5,401,832) and Kordyum, et al. (US Patent No. 6,773,899).

This ground of rejection is believed to be moot in view of Applicant' cancellation of claims 12, 17 and 37.

Rejection under 35 U.S.C. § 103(a) (Fasol, Linemeyer, and Kordyum)

Claims 1, 12, 17, 23-27, 34, and 36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fasol, et al. (J. Thorac. Cardiovasc. Surg. 1994, Vol. 107: 1432-1439), Linemeyer, et al. (US Patent No. 5,401,832) and Kordyum, et al. (US Patent No. 6,773,899).

Fasol, et al. teach application of α-ECGF in a fibrin glue implant in non-ischemic tissue in Lewis rats. Implantation is between the aorta and the myocardium of the left ventricle (see last two lines of page 1).

Fasol, et al. do not teach treatment of human subjects

Fasol, et al. use Lewis rats as their model system (page 4, 3rd full paragraph), not human subjects.

Fasol, et al. do not teach injection into an ischemic region

Fasol, et al. do not teach treatment of ischemic tissue as claimed. Fasol, et al. "did not choose the model of induced angiogenesis in ischemic myocardial tissue beds to avoid possible angiogenic effects of endogenous biochemical agents released by such ischemia-injured tissue" (page 9 of 14, first full paragraph). In contrast, claim 1 is drawn to injection "into the ischemic region of the myocardium".

Fasol, et al. do not teach increased cardiac efficiency

Fasol, et al. do not teach any improvement in cardiac efficiency. In fact, Fasol, et al. specifically state that "we do not have any information concerning the hemodynamic significance of these new blood vessels in supplying blood to the heart". Thus, while formation of new blood vessels was observed, the clinical significance of these new blood vessels was not evaluated.

In contrast, in the present application, patients with coronary heart disease having elective bypass surgery were given FGF during the operation and compared to a control group which received heat-denatured FGF during the surgery as described in application no. 60/093,962, ("provisional application") at page 23, first full paragraph and present application at paragraph 0148. As stated in the application "angiogenic evidence of neovascularization was supported by enhanced ejection fractions in patients receiving hFGF-1, three years after surgery" (provisional application, page 25, lines 7-8; present application, paragraph 0155). As explained in A-Z Health Guide from WebMD (Attachment A), ejection fraction is a measurement of the heart's efficiency. Further explanation of the term "ejection fraction" is provided from the Mayo Clinic website (Attachment B). Accordingly, the patients receiving the FGF were improved in "at least

one clinical index of cardiac function to confirm that the cardiac efficiency has increased" as now claimed (claim 1).

Also, as stated in the application, "patients improved from NYHA III classification before the operation to NYHA I-II three years post-op. The marked improvement in cardiac fuction [sic] three years after growth factor therapy was suprising [sic] in view of the frequent incidence of restenosis in such patients" (provisional application, page 25, lines 19-22; present application, paragraph 0155). (See Attachment C for description of NYHA Classifications). Thus, patients receiving FGF injection were improved by at least two clinical indices of cardiac function, as far out as three years after the surgery. The present claims have been amended to recite a step of "(c) evaluating at least one clinical index of cardiac function to confirm that cardiac efficiency has increased". Support for this amendment is found in the provisional application at page 25, lines 7-22 and in paragraph 0155 of the present application.

Linemeyer, et al and Kordyum, et al.

The deficiencies of Fasol, et al. are not overcome by either Kordyum or Linemeyer, taken separately or together. Linemeyer, et al. and Kordyum et al. teach specific FGF sequences. Linemeyer, et al and Kordyum et al. merely describe that their recombinant FGF is active in an in vitro angiogenesis bioassay in chicken eggs (Example 11 of Linemeyer, et al and Example 6 of Kordyum, et al.). However, neither Linemeyer, et al. nor Kordyum et al. teach evaluation of at least one clinical index of cardiac function. Neither Linemeyer, et al. nor Kordyum et al. teach injection into an ischemic region in humans.

Likelihood of success

There was no likelihood of success that the neoangiogenesis observed by Fasol, et al. for rats could be reproduced in human patients. Fasol, et al. deliberately did not inject α-ECGF into ischemic tissue. Accordingly, there was no expectation, based upon Fasol, et al., that injection into ischemic tissue that might be damaged or necrotic, would result in neoangiogenesis. There was no reason to believe that ischemic tissue would be responsive to injection by FGF in view of Fasol, et al.

Further evidence that it could not have been predicted at the time of the claimed invention that injection of FGF into human subjects in an ischemic region would be successful is provided by Banai, et al. Banai, et al. is of record and was cited in previous Office Actions.

Banai, et al. were unsuccessful in achieving angiogenesis by administration of FGF in dogs. The following are quotes taken from their Discussion on page 84, col. 1:

"Unfortunately, in our preparation, no arteriographic or microscopic evidence of blood vessel formation was found after 4 weeks."

"Thus, the acidic-FGF-treated sponges failed to exert significant angiogenic properties in the canine mediastinum in this model. The primary aim of our study was to assess the angiogenic potential of acidic FGF on the myocardium, and we would be reluctant to extrapolate our finding to the therapy of acute myocardial infarction."

"Thus, no conclusions can be drawn from our observation regarding the potential role of acidic FGF in the treatment of myocardial infarction. However, our results do suggest that careful studies need to be performed before it can be concluded that acidic FGF has either a salutary or a detrimental effect in this situation."

"Although SMC proliferation is an integral part of an angiogenic response, the creation of myocardial vessels undoubtedly requires a complex series of events that is not mimicked by simple exposure of ischemic myocardium to acidic FGF."

In the case of Banai, et al. treatment of ischemic tissue with FGF failed to produce the desired neoangiogenesis. At the time of the claimed invention there was no likelihood of success that injection into an ischemic region of myocardium would produce new blood vessels. While Fasol, et al. report new blood vessel formation by application of α-ECGF in a fibrin glue implant in non-ischemic tissue in Lewis rats, they do not draw any conclusions on the hemodynamic significance of this result in supplying blood to the heart. Certainly there was no likelihood of success at the time of the claimed invention in view of the teaching of Banai, et al. who report failure to observe new blood vessel formation when FGF is administered to ischemic tissue.

Furthermore, as discussed above, Fasol, et al. do not provide any data on improved cardiac function as determined by clinical indices. In contrast, claim 1 as amended includes the

step of "evaluating at least one clinical index of cardiac function to confirm that cardiac efficiency has increased". As discussed above, both the present application and the earlier provisional application report that patients receiving FGF had improved ejection fraction compared to the control patients three years after surgery and improvement in activity level (mild or no limitations on activity as measured by the NYHA classification). Fasol, et al does not provide a reasonable expectation that cardiac function will improve to any extent because the work of Fasol, et al. is limited to injection of rats in non-ischemic regions and clinical indices of cardiac function were not determined.

In conclusion, there was no likelihood of success that injection of FGF into ischemic myocardium in human subjects would produce new blood vessel formation in view of the conflicting results of Fasol, et al. and Banai, et al. While Fasol, et al. were successful in inducing angiogenesis in non-ischemic tissue, Banai, et al. failed to observe neoangiogenesis by similar treatment of ischemic tissue. Additionally none of the cited references teach the step of "(c) evaluating at least one clinical index of cardiac function to confirm that cardiac efficiency has increased" as now claimed.

In view of Applicant's amendment and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

New grounds of rejection

Rejection under 35 U.S.C. § 102(e) (Ellis)

Claims 1 and 24 are rejected under 35 U.S.C. § 102(e) as anticipated by Ellis, et al. (US Patent No. US Patent No. 6,045,565).

Ellis, et al. teach a device and method for boring holes into the myocardium. Angiogenic material may be introduced into the holes. The disclosure of Ellis, et al. is directed primarily to the device for puncturing the endocardium through to the myocardium. Holes are cut as described in col. 5, lines 7-19 of Ellis, et al. Insertion of material, such as "growth factor drug" is described in col. 5, lines 26-37. Ellis, et al. do not teach injection into an ischemic region and do not teach a step of "(c) evaluating at least one clinical index of cardiac function to confirm that cardiac efficiency has increased" after injection of recombinant FGF. Support for the amendment is found in the provisional application at page 25, lines 7-22 and in paragraph 0155

of the present application. Additionally, Ellis et al. do not test in humans. In summary, Ellis, et al. do not teach injection into an ischemic region, do not teach evaluation of at least one index of cardiac function and do not test in humans. Accordingly, Ellis, et al. do not anticipate the presently claimed invention.

In view of Applicant' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a) (Schumacher, Kordyum, and Linemeyer)

Claims 12, 17, and 37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Schumacher, et al. (Circulation, Feb. 1998, Vol. 97: 645-650), Kordyum, et al. (US Patent No. 6,773,899) and Linemeyer, et al. (US Patent No. 5,401,832).

This ground of rejection is moot in view of Applicant's cancellation of claims 12, 17, and 37.

Rejection under 35 U.S.C. § 103(a) (Ellis, Kordyum, and Linemeyer)

Claims 1, 12, 17, and 37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ellis, et al. (US Patent No. 6,045,565), Kordyum, et al. (US Patent No. 6,773,899) and Linemeyer, et al. (US Patent No. 5,401,832).

This ground of rejection is moot for claims 12, 17, and 37 in view of Applicant's cancellation of claims 12, 17, and 37.

Regarding claim 1, as discussed above, Ellis, et al. teach a device and method for boring holes into the myocardium. Angiogenic material may be introduced into the holes. The disclosure of Ellis, et al. is directed primarily to the device for puncturing the endocardium through to the myocardium. Holes are cut as described in col. 5, lines 7-19 of Ellis, et al. Insertion of material, such as "growth factor drug" is described in col. 5, lines 26-37. Ellis, et al. do not teach injection into an ischemic region and do not teach a step of "(c) evaluating at least one clinical index of cardiac function to confirm that cardiac efficiency has increased" after injection of recombinant FGF. Support for the amendment is found in the provisional application at page 25, lines 7-22 and in paragraph 0155 of the present application. Additionally,

Ellis et al. do not test in humans. In summary, Ellis, et al. do not teach injection into an ischemic region, do not teach evaluation of at least one index of cardiac function and do not test in humans.

The deficiencies of Ellis, et al. are not overcome by either Linemeyer or Kordyum, taken separately or together. Linemeyer, et al. and Kordyum et al. teach specific FGF sequences. Linemeyer, et al and Kordyum et al. merely describe that their recombinant FGF is active in an in vitro angiogenesis bioassay in chicken eggs (Example 11 of Linemeyer, et al and Example 6 of Kordyum, et al.). However, neither Linemeyer, et al. nor Kordyum et al. teach evaluation of at least one clinical index of cardiac function. Neither Linemeyer, et al. nor Kordyum et al. teach injection into an ischemic region in humans.

Likelihood of success

As discussed above for the rejection based upon Fasol, et al., there was no likelihood of success that injection into ischemic tissue that might be damaged or necrotic, would result in neoangiogenesis based upon the combination of references cited above. There was no reason to believe that ischemic tissue would be responsive to injection by FGF.

None of the cited references provide any data on improved cardiac function as determined by clinical indices. In contrast, claim 1 as amended includes the step of "evaluating at least one clinical index of cardiac function to confirm that cardiac efficiency has increased". As discussed above, both the present application and the earlier provisional application report that patients receiving FGF had improved ejection fraction compared to the control patients three years after surgery and mild or no limitations on activity as measured by the NYHA classification. The cited references, taken separately or together, do not provide any reasonable expectation that cardiac function will improve to any extent because the disclosure of Ellis, et al. is drawn to a device for puncturing cardiac tissue and the secondary references are directed to FGF sequences. Injection into ischemic regions and clinical indices of cardiac function were not determined.

Further evidence that it could not have been predicted at the time of the claimed invention that injection of FGF into human subjects in an ischemic region would be successful is provided by Banai, et al. Banai, et al. is of record and was cited in previous Office Actions.

Banai, et al. were unsuccessful in achieving angiogenesis by administration of FGF in dogs. The following are quotes taken from their Discussion on page 84, col. 1:

"Unfortunately, in our preparation, no arteriographic or microscopic evidence of blood vessel formation was found after 4 weeks."

"Thus, the acidic-FGF-treated sponges failed to exert significant angiogenic properties in the canine mediastinum in this model. The primary aim of our study was to assess the angiogenic potential of acidic FGF on the myocardium, and we would be reluctant to extrapolate our finding to the therapy of acute myocardial infarction."

"Thus, no conclusions can be drawn from our observation regarding the potential role of acidic FGF in the treatment of myocardial infarction. However, our results do suggest that careful studies need to be performed before it can be concluded that acidic FGF has either a salutary or a detrimental effect in this situation."

"Although SMC proliferation is an integral part of an angiogenic response, the creation of myocardial vessels undoubtedly requires a complex series of events that is not mimicked by simple exposure of ischemic myocardium to acidic FGF."

In the case of Banai, et al. treatment of ischemic tissue with FGF failed to produce the desired neoangiogenesis. At the time of the claimed invention there was no likelihood of success that injection into an ischemic region of myocardium would produce new blood vessels. One cannot conclude from Ellis, et al. that application of FGF to ischemic tissue would improve cardiac efficiency because Ellis et al. do not teach injection of FGF to an ischemic region and do not measure any clinical index of cardiac efficiency. Certainly there was no likelihood of success at the time of the claimed invention in view of the teaching of Banai, et al. who report failure to observe new blood vessel formation when FGF is administered to ischemic tissue.

In conclusion, there was no likelihood of success that injection of FGF into ischemic myocardium in human subjects would produce new blood vessel formation in view of the failure of Banai, et al. to observe neoangiogenesis treatment of ischemic tissue with FGF. Additionally

none of the cited references teach the step of "(c) evaluating at least one clinical index of cardiac function to confirm that cardiac efficiency has increased" as now claimed.

In view of Applicant's amendment and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

CONCLUSION

In view of Applicant's amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Oct. 23 2006

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ATTACHMENT A

October 11, 2006

A-Z Health Guide from WebMD

healthwise

Ejection fraction

The ejection fraction is a measurement of the heart's efficiency and can be used to estimate the function of the left ventricle, which pumps blood to the rest of the body.

The left ventricle pumps only a fraction of the blood it contains. The ejection fraction is the amount of blood pumped divided by the amount of blood the ventricle contains. A normal ejection fraction is more than 55% of the blood volume. If the heart becomes enlarged, even if the amount of blood being pumped by the left ventricle remains the same, the relative fraction of blood being ejected decreases. For example:

- A healthy heart with a total blood volume of 100 mL that pumps 60 mL to the aorta has an ejection fraction of 60%.
- A heart with an enlarged left ventricle that has a total blood volume of 140 mL and pumps the same amount (60 mL) to the aorta has an ejection fraction of 43%.

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Ejection fraction **Previous | Next**

Last updated: May 27, 2005

Print-Friendly Version

ASK A HEART DISEASE SPECIALIST

Oct 11, 2006

Ejection fraction: What does it measure?

ARTICLE TOOLS

Print

Larger type

What does the term "ejection fraction" mean? What does it measure?

- No name given/ Florida

Mayo Clinic cardiologist **Martha Grogan, M.D.,** and colleagues answer select questions from readers.

Answer

During each heartbeat cycle, the heart contracts and relaxes. When your heart contracts (systole), it ejects blood from the two pumping chambers (ventricles). When your heart relaxes (diastole), the ventricles refill with blood. No matter how forceful the contraction, it doesn't empty all of the blood out of a ventricle. The term "ejection fraction" refers to the percentage of blood that's pumped out of a filled ventricle with each heartbeat. This measures the capacity at which your heart is pumping.

Because the left ventricle is the heart's main pumping chamber, ejection fraction is usually measured only in the left ventricle (LV). A normal LV ejection fraction is 55 percent to 70 percent. The ejection fraction may decrease when the heart muscle has been damaged, such as due to:

- Heart attack
- Heart-muscle disease (cardiomyopathy)
- Heart valve problems

A doctor can measure ejection fraction by several methods, including:

- An ultrasound of the heart (echocardiography)
- Cardiac catheterization (left ventriculogram)
- A magnetic resonance imaging (MRI) scan of the heart
- A nuclear medicine scan (multiple gated acquisition, or MUGA) of the heart
- A computerized tomography (CT) scan of the heart

By Mayo Clinic Staff
Sep 19, 2006

New York Heart Association (NYHA) Classification:

A functional and therapeutic classification for prescription of physical activity for cardiac patients.

- Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.
- Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
- Class III: patients with marked limitation of activity; they are comfortable only at rest.
- Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.